REMARKS

The applicants previously amended claim 21 to incorporate all the limitations of claim 23 (which was canceled) because the Office had stated that claim 23 was free of the prior art. As the Office has now reversed itself, the applicants herein reverse their previous amendment, removing the phrase "the inactivated polio virus is mixed with the other components without being adsorbed onto an aluminum salt" from claim 21 and adding new claim 45. New claim 45 corresponds to canceled claim 23.

Claims 21, 22, 24-27 and 29-44 are rejected as obvious under 35 U.S.C. § 103(a) over Petre *et al.* (WO 93/24148) in view of Arminjon AU 708777. For the reasons detailed in their previously-filed appeal brief and responses, as well as the additional arguments and evidence submitted herewith, the applicants respectfully traverse and assert that these claims and new claim 45 are non-obvious over the cited art.

The cited art, alone and in combination, fails to teach or suggest each and every limitation of the claims, and it fails to provide the ordinary artisan with a reasonable expectation of success.

The prior art does not provide a ***particularized*** *suggestion or motivation to make the claimed invention*

First, with regard to claims 21, 22, 24-27 and 29-45, the Office has failed to identify where in the cited art there is a suggestion to combine all the antigens recited in the present claims into a single composition in the manner described in the claims. The Office notes that Petre teaches multi-component vaccine compositions comprising "various antigens, including diphtheria, tetanus, pertussis (toxoid arid filamentous hemagglutiniri), hepatitis B surface antigen (HBsAg), IPV (inactivated polio virus) and HiB (*H influenzae* type B), (abstract, and page 4, lines 10-36)." Office Action p. 1, ll. 2-4. But the teachings to which the Office points relate to various sub-combinations of antigens; the teachings are not directed to the combination of all the antigens recited in claim 21 combined in the manner recited in claim 21. Nor does the Office allege that Arminjon provides the requisite suggestion to combine all the particular antigens of the present claims as described in the claims.

The law requires that the suggestion or motivation that forms the basis of an obviousness rejection be particularized, directed to the invention being claimed; a general motivation or suggestion is simply insufficient. This exact proposition was directly addressed by the Federal Circuit in *In re Lee*, 61 USPQ2d 1430, 1432 (Fed. Cir. 2002), where the court flatly rejected the Patent Office Board of

McDonnell Boehnen Hulbert & Berghoff LLP
300 South Wacker Drive
Chicago, IL 60606
Tel: 312-913-0001

Patent Appeals position that "The conclusion of obviousness may be made from common knowledge and common sense of a person of ordinary skill in the art without any specific hint or suggestion in a particular reference." The court stated

> When patentability turns on the question of obviousness, the search for and analysis of the prior art includes evidence relevant to the finding of whether there is a teaching, motivation, or suggestion to select and combine the references relied on as evidence of obviousness. The factual inquiry whether to combine references must be thorough and searching. It must be based on objective evidence of record. This precedent has been reinforced in myriad decisions, and cannot be dispensed with. The need for specificity pervades this authority.

Id. at 1434 (citations omitted). *See also In re Deuel*, 34 U.S.P.Q.2d 1210, 1215 (Fed. Cir. 1995) (the prior art must suggest the particular form of the invention and how to make it; general guidance is insufficient); *In re Rouffet*, 47 USPQ2d 1453, 1459 (Fed. Cir. 1998) ("even when the level of skill in the art is high, the Board must identify specifically the principle, known to one of ordinary skill, that suggests the claimed combination. In other words, the Board must explain the reasons one of ordinary skill in the art would have been motivated to select the references and to combine them to render the claimed invention obvious."); and *In re Obukowicz*, 27 U.S.P.Q.2d, 1063, 1065 (Bd. Pat. App. Int. 1992) (Prior art "that gives only general guidance and is not at all specific as to the particular form of the claimed invention and how to achieve it . . . does not make the invention obvious.").

The applicants respectfully submit that the Office has failed to identify in the prior art a suggestion or motivation to make a composition with the particular combination of antigens presently recited, nor make the claimed composition in the manner recited. Rather, the Office has identified elements of the present claims scattered throughout Petre *et al.* and Arminjon *et al.* without identifying specific teachings to bring all the elements together. The applicants respectfully submit that this amounts to nothing more than hindsight reconstruction of the present claims.

Without a particularized suggestion or motivation to make the claimed invention, the obviousness rejection cannot stand.

With regard to new claim 45 (in addition to the foregoing), Petre *et al.* teaches that in the formulation of a multivalent vaccine including a Hepatitis B surface antigen (HBsAg), ***all*** the components of the vaccine composition are to be adsorbed onto a suitable adjuvant:

> 1. Avoiding the use of AH [aluminum hydroxide] to adsorb the HBsAg component in the vaccine formulation [of the invention] also gives rise to a product of markedly superior stability.
>
> ...

McDonnell Boehnen Hulbert & Berghoff LLP
300 South Wacker Drive
Chicago, IL 60606
Tel: 312-913-0001

Preferably the HBsAg is adsorbed on AP [aluminum phosphate]. In particular we have found in human clinical studies that when **AP-adsorbed HBsAg is combined with one or more AH-adsorbed or AP-adsorbed antigens** in a combined vaccine no substantial decrease in immunogenicity occurs.

P. 2, ll. 31-34.

2. In a further aspect, the invention provides a combined vaccine comprising Hepatitis B surface antigen (HBsAg) adsorbed to AP and an antigen adsorbed to AP or to AH selected from an antigen providing immunity against one or more of the following viruses...

   P. 3, ll. 8-11.

3. In general, the combined vaccine compositions according to any aspect of the invention can be prepared as follows. The required DT, DTPw, DTPa, HA or other components are adsorbed onto a suitable adjuvant, especially AH or AP; HBsAg is adsorbed onto a suitable stabilizing adjuvant, selected as hereinabove described, especially an aluminum salt other than AH. Preferably it is adsorbed onto AP. After allowing time for complete and stable adsorption of the respective components, the different components are combined under appropriate conditions.

   p. 8, l. 35, through p. 9, l. 3.

4. Every Example in Petre *et al.* teaches embodiments in which **all** the antigens are adsorbed onto an aluminum salt.

The Office points to claim 27 of Petre *et al.* as teaching that only one of the components in the multivalent vaccine is adsorbed to an aluminum salt and the others are not. The applicants respectfully disagree. First, claim 27 merely teaches a composition comprising HBsAg adsorbed to aluminum phosphate having greater stability than the corresponding vaccine in which HBsAg is adsorbed to aluminum hydroxide. That is, claim 27 is drawn to the inventive feature taught in the specification, which is avoidance of aluminum hydroxide as an adjuvant for HBsAg and the use of other HBsAg adjuvants, such as aluminum phosphate (as indicated in numbered item 1, above). Claim 27's teachings are directed only to the nature of the HBsAg antigen in the claimed composition. It neither teaches nor suggests that the other antigens in a multivalent HBsAg vaccine are not adsorbed onto an adjuvant.

Nor, for the very same reasons just discussed, do claims 6 and 7 (also cited in the present Office Action) teach or suggest that the antigens other than HBsAg need not be adsorbed onto an adjuvant. Claims 6 and 7 both ultimately depend from claim 1, which recites, in part, "A combined vaccine composition comprising Hepatitis B surface antigen (HBsAg) and a number (n) of other antigens **in combination with an adjuvant comprising one or more aluminum salts**..." (emphasis added).

Claim 6 merely further limits claim 1 by requiring that the composition comprises an antigen adsorbed to AH selected from diphtheria, tetanus, pertussis, inactivated Polio, Haemophilus influenzae b, and Hepatitis A. And claim 7 recites a composition comprising HBsAg and at least two antigens. There are no teachings in claims 6 and 7 regarding adsorption onto an aluminum adjuvant that differ from the teachings in the remainder of the publication (which are that **all** antigens are adsorbed onto an aluminum salt).

The significance of claim 6 is that it limits the claimed composition to those having an antigen other than HBsAg adsorbed to "AH [aluminum hydroxide]". That is, the purpose of the claim is to limit the **type** of aluminum salt to which one of the antigens is adsorbed, the presumption being that all antigens are adsorbed onto an aluminum salt. Claim 6 does not recite that the antigen is adsorbed to "an adjuvant," which indeed may have suggested that other antigens need not be adsorbed onto an adjuvant.

In summary, there are no teachings in Petre *et al.* (or Arminjon *et al.*) suggesting a composition in which inactivated polio virus is not adsorbed onto an aluminum salt. Nor does the art taken as a whole suggest a composition as presently claimed in which inactivated polio virus is not adsorbed onto an aluminum salt. So, for this reason as well, claim 45 cannot be obvious over the cited art.

The cited are does not imbue the ordinary artisan with a reasonable expectation of success

The Office asserts on page 5 of the Office Action that "[o]ne would have had a reasonable expectation of success that the antigens of Arminjon would have been successfully incorporated into Petre's vaccine because multi-component stable vaccines are known, as evidenced by Petre and Arminjon." The applicants respectfully disagree.

The applicants respectfully submit that the rationale used by the Office is simply incorrect. To conclude that one would have a reasonable expectation of success with the presently claimed composition because multi-component stable vaccines are known in the art is either (a) to assume that all multi-component vaccines would be expected to be stable and effective, regardless of the number of valencies and their identity, or (b) simply ignore those multivalent compositions that manifested antigenic competition and lead to the commonly accepted recognition of the phenomenon. This selective reading of the prior art is improper.

Combining several antigenic valencies in an immunogenic composition has long been recognized as problematic by those skilled in the art due to the phenomenon of antigenic competition. This phenomenon manifests itself in the diminution of immunogenicity of one or more components when

combined with other antigens. Of course not all combinations of antigens suffer this fate, but one skilled in the art cannot determine *a priori* whether any particular combination will. And the phenomenon is sufficiently prevalent that one of ordinary skill in the art could not have a reasonable expectation of success when combining antigens in a multivalent immunogenic composition, especially with a large number of valences as in the presently claimed compositions.

Arminjon *et al.* teaches multivalent vaccines compositions in Examples 12 and 13, but reports only on the stability of the PRP-T component in Example 12 and, in Example 13, the stability and immunogenicity of the PRP-T component and the immunogenicity of the Hbs component. Arminjon *et al.* does not report on the immunogenicity of the other components and, therefore, provides no teachings as to whether antigenic competition detrimentally affected the other components.

The prior art not only recognized the difficulty of combining antigens in general, it also recognized the difficulty in combining the antigens recited in the present claims. The applicants previously presented three prior art references that manifested the uncertainty associated with combining multiple antigens in a single composition, which are summarized below:

1. Eskola, *J. Infectious Diseases* **174**, S302-5 (1996) ("Eskola I")

Addressing a DTaP-Hib vaccine, Eskola I states in the introduction:

> Combined vaccines cannot, however, be made by simply mixing vaccines in the same syringe. One must take into consideration all constituents, including stabilizers, preservatives, and adjuvants, and their relative properties and potential chemical and biologic interactions.

p. S302, col. 1 (emphasis added). And in the section entitled, "Implications for the Future," (pp. S304-S305), Eskola states:

> In the next few years, data from vaccine trials will affect the development of combined vaccines. Evidence of the protective efficacy and clinical usefulness of Pa [acellular pertussis] vaccines will be available soon. National vaccination programs will probably start using DTPa instead of DTPw [whole cell pertussis], and new combined vaccines, such as DTPa-Hib and DTPa-IPV-Hib, may become available.
>
> From experience with DTPw-Hib combinations, one could expect interference between Hib, diphtheria, tetanus, and pertussis antigens in the new DTPa-Hib combined vaccines. The clinical significance of this interference must be considered carefully.

(Emphasis added.)

2. Eskola *et al.*, *The Lancet* **348**, 1688 (1996) ("Eskola II")

Eskola II reported that the mixture of DTaP, IPV, and Hib interferes with the primary antibody response to poliovirus antigens and, to a much greater extent, Hib, characterizing the immunogenic response to Hib as "poor." *Id.* at 1690. Eskola II noted that three other studies reported significantly lower concentrations of antibodies to Hib in groups receiving mixed DTaP Hib conjugate vaccines compared to groups to which the various vaccines were administered separately. Eskola stated that "[t]he mechanism by which mixing of the vaccines reduced the antibody response is not clear." *Id.* at 1691.

3. Bell *et al.*, *Vaccine* **16**, 637 (1998)

Bell *et al.* administered a combination vaccine of DPT-a (diphtheria, tetanus, acellular pertussis (pertussis toxin + filamentous haemagglutinin)) absorbed with aluminum hydroxide and mixed with PRP-T. It reported a decrease in Hib antibody titers compared to when the PRP-T is administered separately. Like Eskola II, Bell *et al.* stated that the explanation for the reduction was unknown, citing five studies reporting similar results.

Furthermore, as previously noted, Bell *et al.* reported Hib antibody titer (GMT (μg/mL) 95% CL of less than 1 whereas the present specification reports 1.46. Bell notes that it has been proposed that the threshold mean Hib antibody titer for continued protection following immunization be raised to 1.0 μg/ml. Thus, the difference in results between Bell *et al.* and the composition of the present application has significance.

While Bell notes that others reported combined DTaP/PRP-T vaccines resulted in Hib GMTs of greater than 1, Bell also reported that these and others consistently observed reduced Hib antibody titer when various Hib vaccines have been combined in the same syringe with aP.

Furthermore, it is of significance that whereas 82% of subjects manifested seroprotection of >0.15 μg/ml Hib antibody after 3 doses of a DTaP/PRP-T vaccine in Bell (*see* Table 1), 92.1% of the subjects administered the presently claimed vaccine manifested the same level of Hib seroprotection, despite receiving a vaccine comprising a greater number of valencies (*see* Table 4). This could not have been anticipated with any reasonable expectation of success.

These publications establish that the art recognizes the obstacles faced by the ordinary artisan when preparing a multivalent vaccine of DTP and Hib. The art both recognizes that antigenic competition (wherein following administration of several antigens the immune response to one or more of them is

suppressed or diminished) is at play in such compositions and, accordingly, the results observed, particularly with regard to the immunogenic response to the Hib conjugate, varies widely and cannot be predicted *a priori* with any reasonable degree of certainty. Eskola II notes that the phenomenon of antigenic competition is not understood.

Given the results of such studies as presented by Eskola II and Bell *et al.*, one of ordinary skill in the art could not have anticipated that the compositions of the present claims would induce Hib antibody titers of > 1 µg/ml and that more than 90% of the population vaccinated would manifest a seroprotective level of Hib antibody.

In a previous Action (mailed February 7, 2005), the Office dismissed the applicants' reliance on the two Eskola articles, stating that they do not teach compositions in which the antigens are adsorbed on aluminum. But the Office failed to provide any basis in the art or scientific reasoning as to why the ordinary artisan would consider the distinction significant and, therefore, not consider the teachings of the two Eskola articles significant in determining whether there would be a reasonable expectation of success. There must be some scientific basis relating the affect (if any) of adsorption on aluminum with antigenic interference to dismiss the two Eskola articles as the Office has done. Yet the Office has provided none. Thus, the Office's dismissal of the teachings of the two Eskola articles is improper. The applicants reiterate that one skilled in the art would consider the Eskola articles as both relevant and as manifesting the art-recognized uncertainty involved vis-à-vis antigenic competition in combining multiple antigens in a single composition. Furthermore, the Office's attention is directed to the discussion of WO 99/48525, below, which does discuss antigenic interference observed with antigens adsorbed on aluminum hydroxide.

In the same Action, the Office gave little more weight to Bell, arguing that Bell did not offer a "conclusive" comment on the antibody titer required to provide protection against Hib and that Bell only suggests raising the Hib antibody titer for continued protection following immunization. The significance of Bell's teaching that the minimum Hib antibody titre of 1.0 µg/ml be adopted for continued protection following immunization with a polysaccharide vaccine is that Bell's compositions, which teach aluminum adsorbed antigens, resulted in Hib antibody titre's of significantly less than 1.0 µg/ml whereas the compositions of the present claims induced a titre of 1.46 µg/ml. Given the significance attached to the 1.0 µg/ml level, this distinction is important, and nothing in the cited art suggests that it could have been expected with a reasonable degree of certainty.

Antigenic interference was also at the basis of the technical problem addressed by Petre, in which there was interference existing among vaccine components in the presence of aluminum hydroxide (AH) (with HBsAg adsorbed on AH), whereas no interference existed when combining HBsAg with HA, DT, DTPw or DTPa. Petre's solution was to adsorb HBsAg first on aluminum phosphate (AP), the other antigens on AH, and then mixing the components. The ordinary artisan would appreciate that this was a specific solution to the specific combination of HBsAg with these other components in the presence of aluminum hydroxide and that the solution was not otherwise generally applicable. Petre does not disclose a solution applicable to all combinations of antigens.

Even if in theory it is possible to adsorb any vaccine component on an aluminum salt, in practice interference and/or lack of vaccine and stability may occur when several components are present, and Petre provides a solution only for a specific combination of antigens and not give a general rule allowing the one skilled in the art to conceive any combination of antigens into a vaccines having no antigenic interference and good stability.

The interference issue was also recognized in WO 99/48525, which is staged on p. 2, ll. 3-14:

> It has been found, however, that simple mixing of the components of a combination vaccine is complicated by the fact that not all antigens can be effectively mixed together. The reduction in the immunogenicity of an antigen when combined with other components (as compared to the particular antigens administered alone) is known as interference. It is known, for example, that the extemporaneous mixing of a DTPa combination vaccine with unadjuvanted Hib results in a reduction of antibody titers to the polysaccharide component of Hib (WO 97/00697). In addition, WO 97/00697 showed that if Hib is adsorbed onto aluminum hydroxide, there is a significant reduction of antibody titers to the polysaccharide component. These results indicated that there was interference between the aluminum hydroxide of the DTPa vaccine and Hib. In order to try and minimize this interference in such an extemporaneously-prepared combination vaccine Hib was pre-absorbed onto aluminum phosphate.

The solution proffered in WO 99/48525 was to pre-absorbed one or more antigens onto aluminum hydroxide, adsorbing Hib and one or more additional antigens onto aluminum phosphate, and then combining them all.

In each of the foregoing instances, the specific solution involved adsorbing Hib onto aluminum phosphate. Each provided a specific solution to the problem of antigenic interference. None, however, taught or suggested the particular combination of antigens recited in the currently pending claims and the method of preparation. Nor based on the prior art could one have had a reasonable expectation of success.

Furthermore, the applicants reiterate their previously-presented position that the results they

achieved are surprising. The Office disagreed in the present Action, asserting that one would have expected the results presented in the specification in view of the reasonable expectation of success. But, as demonstrated above, there was no reasonable expectation of success given the empirical data and conclusions of the published authors (*e.g.*, "From experience with DTPw-Hib combinations, one could expect interference between Hib, diphtheria, tetanus, and pertussis antigens in the new DTPa-Hib combined vaccines." Eskola I). And the Office has failed to provide any scientifically based rationale as to why one of ordinary skill in the art would have had a reasonable expectation of achieving the results observed with the compositions of the present claims. The applicants respectfully submit that the burden is on the Office to do so.

In conclusion, because (a) the prior art fails to provide a particularized teaching or suggestion to make the presently claimed methods and compositions comprising each of the recited antigens, (b) the prior art fails to imbue the ordinary artisan with a reasonable expectation of success (*i.e.*, that the multivalent compositions of the claims would not exhibit antigenic competition), (c) the lack of antigenic competition was unexpected, and the Hib antibody titer is greater than one skilled in the art could have predicted with a reasonable degree of certainty, the presently claims cannot be obvious. Accordingly, the Applicants respect-fully request reconsideration and withdrawal of this rejection.

Respectfully submitted,

Date: March 17, 2006

Michael S. Greenfield
Registration No. 37,142